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EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	**PAPER NUMBER**
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/715,764	LENZ ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *31 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47,48,50,52-54,56,57 and 59-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47,48,50,52-54,56,57 and 59-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Currently, claims 47-48, 50, 52-54, 56-57, and 59-67, are pending in the instant application. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. The following office action contains new grounds of rejection. The rejections set froth below constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is Non-Final.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. It is noted that a few amendments have been made to the claims which are not properly reflected, see for example claim 66, the recitation of "wherein the" is underlined but was present in the previous amendment. Applicant is asked to carefully note which amendments are being made and to accurately reflect the status of amended and non amended subject matter in any future claim submissions.

4. The rejection under 35 USC 103, made at section 15 of the previous office action is withdrawn as it is redundant in view of the rejection made at section 12 below.

Claim Rejections - 35 USC § 112

Written Description

5. Claim 67 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

Claim 67 recites "wherein the subject suffers from a cancer selected from ... metastatic liver cancer *associated* with disseminated colon cancer". The response sites the specification at page 14, as providing support for the amendment. While the specification teaches analysis of "metastatic liver cancer in patients with disseminated colon cancer", the specification provides no recitation of "associated". This term is broader as it does not limit the metastatic liver samples from those in patients with disseminated colon cancer. The specification does not provide any teaching or guidance regarding the term "associated" when used in this concept. Accordingly, the specification as originally filed does not to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

6. Claims 47-48, 50, 52-54, 56-57, and 59-67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for screening a human subject for sensitivity to 5-FU comprising determining the genotype of a subject's biological sample at a tandemly repeated 28 base pair repeat in the 5' UTR of a TS gene in the sample and correlating

said genotype to 5-FU, does not reasonably provide enablement for screening any subject for sensitivity to any TS-directed chemotherapeutic drug comprising determining the genotype of a subject's biological sample at a tandemly repeated 28 base pair repeat in the 5' UTR of a TS gene in the sample and correlating said genotype to said sensitivity to said TS-directed chemotherapeutic drug. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims broadly encompass screening any subject for sensitivity to any TS directed chemotherapeutic drug by genotyping the subject's 28 base repeat in the 5' UTR of thymidylate synthase and correlating the genotype to sensitivity to the drug. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

The specification teaches a study which correlated a human subject's thymidylate synthase 5'UTR 28 base pair repeat genotype with TS mRNA expression in normal and tumor cells (see pages 14-15). Further, the art teaches a correlation between TS mRNA expression and sensitivity to 5-FU. The specification teaches (page 5) that TS is the enzyme that catalyzes the intracellular methylation of dUMP to dTMP, which is the sole *de novo* source of thymidylate, and is a critical target for 5-fluorouracil which binds to TS and inhibits the conversion of dUMP to dTMP. The specification teaches that therefore, sensitivity or resistance to 5-FU is dependent on levels of TS in tumors. Accordingly, the specification is enabling for a method for screening a human subject for sensitivity to 5-FU comprising determining the genotype of a subject's biological sample at a tandemly repeated 28 base pair repeat in the 5' UTR of a TS gene in the sample and correlating said genotype to said sensitivity to 5-FU.

However, the specification broadly defines "TS-directed drug" to encompass drugs that involve or are targeted against, or are based on thymidylate synthase. This encompasses an extremely large group of drugs, including any fluoropyrimidine, which have not been taught by the specification. The specification provides no universal correlation that any drug which involves, targets, or is based on TS would be sensitive to the levels of TS in tumors. Without such guidance the skilled artisan would be unable to predictably determine which other TS directed drugs would also be associated with sensitivity to chemotherapy given that the claims encompass a large class of drugs which are not functionally related and the specification provides no guidance as to other classes of drugs which would function in the same manner as a fluoropyrimidine. The large genus of drugs that "are based" on TS or involve TS, or even target TS, as encompassed by the claims, would not be expected to do so by the same mechanism as a

5-FU which specifically binds to and inhibits TS. The claimed drugs include a large genus of drugs which are structurally and different from each other and from 5-FU. Additionally, the claims encompass screening in any subject, which includes other mammals such as dogs, but the specification only provides analysis of the TS 5'UTR 28 base pair repeat in humans. The specification provides no guidance as to whether the repeat occurs in other species, such as dogs.

Papamichael (The Oncologist, vol. 4, 1999, pages 478-487) teaches that 5-FU is characterized by marked schedule dependency in both the quality and quantity of its effects (page 480). Papamichael teaches that a number of other fluoropyrimidines have been synthesized, such as doxifluridine which must have its ribosyl group removed by the enzyme uridine phosphorylase to produce 5-FU (page 482, col. 1, 2nd full para). Papamichael teaches that this enzyme is reported to be more activity in some tumor cells than in normal tissues, resulting in an improved ratio in tumor bearing mice, but that very high activity is found in normal human liver casting doubt on doxyfluridine's claimed sensitivity.

To identify and determine which drugs encompassed by the broad scope of the claims would be associated with an sensitivity based on the TS polymorphism of any subject would require extensive experimentation which, given the lack of guidance in the specification, would essentially be random, trial by error experimentation, which is considered to be undue. While methods for identifying polymorphisms are known in the art, such methods provide only the general guidelines that allow researchers to randomly search for mutations that may linked to a disease or therapeutic response. The results of performing such methodology is highly unpredictable. The specification does not provide a predictable means for identifying additional drugs which are associated with sensitivity based on the TS genotype of any subject. The art of

determining an association between a polymorphism and response to treatment is highly unpredictable. An association between a polymorphism and treatment response to one type of drug does not allow one to reasonably predict whether the polymorphism will also be associated with responses to other types of drugs. Accordingly, there is no predictable means for ascertaining a priori whether the TS genotype will be associated with sensitivity using other types of "TS directed" chemotherapeutic drugs, as is broadly defined by the specification.

In the instant case, the claims do not bear a reasonable correlation to the scope of enablement because the specification teaches only an association between the TS 5'UTR 28 base pair repeat polymorphism in humans and sensitivity to 5-FU whereas the claims encompass using the TS genotype to correlate sensitivity to any type of TS directed chemotherapeutic drug in any species. The specification has not taught that the TS genotype is associated with a representative number of different types of TS directed chemotherapeutic drugs as is broadly defined. As set forth above, in view of the unpredictability in the art, extensive experimentation would be required to determine whether the TS 5'UTR 28 base pair repeat polymorphism is associated with sensitivity to any fluoropyrimidine let alone any "TS directed chemotherapeutic drug". Accordingly, although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

Indefinite

7. Claims 57-60, 61, 63, and 66-67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 57 recites "means for determining a genomic polymorphism", however the function of 'determining a genomic polymorphism' is vague because it can include a number of different functions: such as amplifying, detecting sizes on a gel, etc. and it cannot be determined what specific function the "means" is drawn to.

Response to Arguments

The response traverses the rejection and points to page 8, lines 11-14, page 14, and figure 1 and asserts that the office is required to look to applicant's specification for structure corresponding to the claimed means. This argument as well as the specification have been thoroughly reviewed but were not found persuasive. At page 8, lines 11-14, the specification recites the term "means", but the examples provided at lines 11-14 are methods with different functions and do not set forth any particular structural requirements for the claimed means. At page 14, the specification again recites a number of different functions which are associated with "determining a genomic polymorphism", for example it discloses DNA extraction using a Qiagen kit, as well as PCR, using primers and undisclosed enzyme. It is therefore, unclear which "means" the claims are limited to.

B) Claim 61 lacks antecedent basis for the term "the subject's biological sample fluid" as there is no previous recitation to a biological sample *fluid.*

Response to Arguments

The response asserts that claim 47 has been amended to provide antecedent basis for claim 61. This argument as well as the amendment have been thoroughly reviewed but were not found persuasive because claim 47 continues to lack proper antecedent basis for the recitation of biological sample *fluid*, no fluid is set forth in claim 47.

C) Claim 59 recites "wherein the kit components may be provided in solution or as a liquid dispersion". The recitation of "may be" renders the claim indefinite as it is unclear if the components are or are not in a solution or as a liquid dispersion".

D) Claim 67 has been amended to recite "metastatic liver cancer *associated* with disseminated colon cancer". The term "associated" is indefinite as it is unclear if it is limited to metastatic liver cancer found in patients with disseminated colon cancer. Alternatively, it is unclear if the recitation encompasses a type of metastatic liver cancer with some of the characteristics of other metastatic liver cancers, for example that found in patients with disseminated colon cancer, but that the claim is not limited to metastatic liver cancer which is found in patients with disseminated colon cancer. The specification does not define the term and therefor the metes and bounds of the claim are unclear.

Claim Rejections - 35 USC § 102

8. Claims 57 and 59 are rejected under 35 USC 102(b) as being anticipated by New England Biolabs catalog (1996, page 102).

This rejection is newly applied to amended claim 57 and claim 59. New England Biolabs teaches a kit which contains a DNA ladder X174 DNA-Hae III Digest which contains base pairs on the order of 1,353 base pairs to 72 base pairs. Alternatively, New England Biolabs teaches a kit which contains a DNA ladder pBR322 DNA-BstN I Digest which contains base pairs on the order of 1, 857 to 13 base pairs (see page 102). Either of these DNA ladders could be used as sequencing markers and appear to be a component of the kit of claim 57. Additionally, the DNA ladder is provided in a solution of 10 mM Tris and 1mM EDTA (claim 59). It is noted that the use for the kit and the instructions for the kit carry no patentable weight as they merely set forth an intended use for the components of the kit. Additionally, the components of the kit could be used for other processes and their use is not dependent on the instructions of the kit. See In re Ngai, 03-1524 (CAFC 2004). The court held that "Here, the printed matter in no way depends on the kit and the kit does not depend on the printed matter. All the printed matter does is teach a new use for an existing product..."

9. Claims 57 and 59 are rejected under 35 U.S.C. 102(b) as being anticipated by Promega Catalog (1997), page 78.

Promega catalog teaches a kit comprising Taq DNA polymerase (means for determining a genomic polymorphism at a tandemly repeated 28 base pair sequence of the 5' UTR of the TS gene; claim 57), dNTPs, storage buffer, and reaction buffer (reagents, components provided in solution or as a liquid dispersion, claims 57 and 59). It is noted that the use for the claimed kit and the instructions for the kit carry no patentable weight as they merely set forth an intended use for the components of the kit. Additionally, the components of the kit could be used for

other processes and their use is not dependent on the instructions of the kit. See In re Ngai, 03-1524 (CAFC 2004). The court held that "Here, the printed matter in no way depends on the kit and the kit does not depend on the printed matter. All the printed matter does is teach a new use for an existing product...".

It is noted that at page 14, the specification asserts "the 5' UTR of the hTS gene was amplified by PCR using the following... as previously described (7)". However, reference 7 is a paper dated from 1974 (see page 16 of the specification) and does not teach PCR. Further, none of the references have been incorporated by reference into the specification. Horie et al; 1995 teaches amplification of the 5'UTR region of hTS using Taq polymerase. Accordingly, absent any specific polymerase set forth at this section, the kit taught by Promega catalog anticipates the claimed kit.

Response to Arguments

10. The response traverses the rejection and asserts that the position is maintained and traversed for the reasons of record. This is confusing as this rejection was not applied before and it is unclear what reasons of record the response refers to. In traversing the rejection under 35 USC 112/2nd paragraph, the response pointed to several areas of the specification as providing examples of means. It is noted that at page 14, the specification discloses PCR, without setting forth any specific enzyme. Taq DNA polymerase is a polymerase used in PCR which is comprised in the kit set forth in Promega catalog.

11. Claims 57 and 59 are rejected under 35 U.S.C. 102(b) as being anticipated by Qiagen Product catalog 1998, page 82.

The claims are drawn to a kit "comprising means for determining a genomic polymorphism". At page 14 of the specification, at "Analysis of TS gene polymorphism", the specification teaches using "the Qiagen kit". Qiagen 1998, teaches a kit for extracting genomic DNA, such as QIAamp Tissue kits which include micropsin DNA columns, reagents, buffers, and proteinase K (claims 57 and 59). It is noted that the use for the claimed kit and the instructions for the kit carry no patentable weight as they merely set forth an intended use for the components of the kit. Additionally, the components of the kit could be used for other processes and their use is not dependent on the instructions of the kit. See In re Ngai, 03-1524 (CAFC 2004). The court held that "Here, the printed matter in no way depends on the kit and the kit does not depend on the printed matter. All the printed matter does is teach a new use for an existing product...".

Claim Rejections - 35 USC § 103

12. Claims 57 and 59-60 are rejected under 35 USC 103(a) as being unpatentable over Horie in view Erlich (US Patent 5,468,613) Baxter-Lowe (Baxter-Lowe et al; US Patent 5,702,885), and New England Biolabs.

Horie teaches a method for analyzing the number of repeats in the 5' UTR of the TS gene using PCR and size analysis on a gel (see page 192, col. 2-page 193; Figure 3). With regard to claim 57, the primers are considered means for determining a genomic polymorphism in the TS 5' UTR. It is further noted that the first primer taught by Horie is identical to instant SEQ ID

NO: 6, and the 2nd primer of Horie "comprises" instant SEQ ID NO: 7 (contains 9 additional nucleotides on the 5' end), which are the primers the specification teaches were used to "determine" the presence of the TS polymorphism. Although the 2nd primer of Horie is not identical to the SEQ ID NO: 7 taught at page 14 of the specification, SEQ ID NO: 7 is 29 nucleotides long. It was known in the art at the time the invention was made that sequences on either end of a primer could be removed and still provide for an effective primer. Baxter-Lowe teaches "Since effective PCR primers usually range between 15-30 nucleotides, it will be appreciated that other effective primers partially including or overlapping the foregoing sequences could be designed." (see col. 25, lines 1-4). Therefor it would have been prima facie obvious to the ordinary artisan at the time the invention was made to modify the antisense primer of Horie by removing nucleotides from the 5' end of the primer to arrive as it was known in the art that "primers partially including or overlapping" already known primers, as well as primers which are 15-30 nucleotides long are effective in PCR amplification.

With regard to claims 57 and 59, Horie teaches using primers, Taq polymerase, dNTPs, and reaction buffer for the PCR reaction, and further teaches analysis on a 4% agarose gel, the use of molecular markers for size analysis, as well as DNA tandemly repeated sequences (claim 60). Horie does not teach packaging these means and reagents in kit format, however Erlich teaches constructing allele specific probes for the purposes of identifying specific alleles in hybridization assays (see abstract, col. 5, lines 32-40) and further, Erlich teaches providing kits which include reagents for identifying alleles in hybridization assay. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to package the reagents taught by Horie, for determining the TS 5' UTR repeat alleles of a subject,

including primers as set forth above, including instant SEQ ID NOS 6 and 7, as well as PCR reagents and reagents for size analysis on a gel, in kit format, for the obvious improvement of providing the reagents taught by Horie in ready to use form, to make the method of detecting the repeats easier and more convenient to perform. The ordinary artisan would have been motivated to provide such an oligonucleotide in kit format for the obvious improvement of provided pre-weighed, premeasured reagents that would make the method of Horie more convenient to perform.

With regard to claim 60, it would have been further obvious to provide either size markers, or the sequences of the different tandemly repeated alleles as positive controls in order to provide a comparison to determine the identity of the alleles detected, and to provide such nucleic acids in a solution of TE buffer as such was commonly used as a nucleic acid storage solution at the time of the invention, as evidenced by New England Biolabs catalog.

It is noted that the use for the kit and the instructions in the kit carry no patentable weight as the instructions are merely printed material which are provided with kits. It is further noted that the temperature of the buffer solution carries no patentable weight as it does not provide any structural limitation to the kit.

Response to Arguments

13. The response traverses the rejection and asserts that it "incorporate[s] by reference the reasons of record why the office has failed to present a prima facie case of obviousness" and further "direct the office's attention to the attached declaration". This argument as well as applicants previous responses and the attached declaration have been thoroughly reviewed but

were found unpersuasive. Of note, none of the previous responses address the teaching of Horie of a specific primers used in the specification (the first primer taught by Horie is identical to instant SEQ ID NO: 6) as noted in the rejection set forth above, as well as reagents which are specifically set forth in specification at page 14. Additionally, the declaration submitted under 25 USC 1.132, by Dr. Peter V. Danenberg does not address any of the kit claims, 57-60.

14. Claims 47-48, 52-54, 56, 64 and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horie and Leichman in view of Ruano,

Horie teaches that triple tandemly repeated sequences are known to exist in the 5' terminal regulatory region of the human TS (thymidylate synthase) gene and that the number of tandemly repeated sequences was found to be polymorphic among individuals (see abstract, and page 191, 2nd column). Horie teaches that the number of repeated sequences was found to result in differences in expression activity of the gene, with the double repeat showing lower expression than the triple repeat (see abstract). Horie teaches detection in leukocytes (blood cells; claim 64) using PCR amplification surrounding the repeat region and determination of the size of amplicons to determine the repeat(s) present (pages 192-193). While Horie teaches that possible mechanisms for expression could occur at either the transcriptional or post transcriptional level, Horie teaches that the unique repeated structure is associated with either possibility (see page 195 column 2, to page 196, column 1, 2nd para). Horie does not teach a correlation between expression of the TS gene and sensitivity to chemotherapeutic drugs, however, Leichman et al disclose a method for determining the suitability of treating cancer in a subject with a chemotherapeutic drug (5-fluorouracil, 5-FU) by taking a biological sample of a

subject and determining expression of the TS gene (see page 3224, page 3226 last para). Leichman teaches that expression levels of TS correlated with sensitivity to 5-FU in the subjects. Leichman teaches that if patients with tumor sensitivity to 5-FU can be identified before the initiation of therapy, 5-FU based treatment could be targeted to that group and would spare toxicity to patients unlikely to respond and would allow faster progress in new drug development.

Ruano teaches that genetic variability is a determinant of a patient's response to therapy. Ruano teaches that by correlating a haplotype with disease and by using genome anthologies, which are collections of a specific locus, as targets for drug screening and development, it is possible to create a prognostic test for customizing therapy based on a patient's genotype (see column 7, lines 3-15). Further, Ruano teaches that different gene variants may be correlated to variable expression levels and that genome anthologies may comprise collections of regulatory sequences (see col. 12, lines 40-42).

Although Leichman does not teach that the expression of TS is correlated to a particular genotype, given the teachings of Horie, in view of Ruano, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to arrive at a method of screening a subject for sensitivity to 5-FU by determining the number of repeats in the 5' regulatory region (genotype) in each allele of the TS gene for the purposes of developing a genotypic assay for determining a subject's response to TS directed chemotherapy drugs. The ordinary artisan would have been motivated to determine if chemotherapy with 5-FU for patients with colorectal cancer could be customized for patients according to their genotype, that is the number of TS repeats, because Ruano teaches to create a prognostic test for customizing therapy

based on a patient's genotype. Further, Leichman also provides motivation for screening as Leichman teaches that if patients with tumor sensitivity to 5-FU can be identified before the initiation of therapy, 5-FU based treatment could be targeted to that group and would spare toxicity to patients unlikely to respond and would allow faster progress in new drug development.

Given that Leichman teaches that expression levels of TS correlated with sensitivity to 5-FU and that Horie teaches that 1) TS expression is associated to the number of tandemly repeated sequences in the 5' terminal regulatory region of the human TS (thymidylate synthase) gene, 2) that the number of tandemly repeated sequences (genotype) was found to be polymorphic among individuals (see abstract, and page 191, 2nd column), and 3) that the number of repeated sequences was found to result in differences in expression activity of the gene, with the double repeat showing lower expression than the triple repeat, it would have been prima facie obvious to the ordinary artisan at the time the invention was made to screen for a subject's sensitivity to 5-FU by determining the genotype of the number of tandemly repeated sequences in the 5' terminal regulatory region of the TS gene obtained from a subject's biological sample for the purpose of providing a genotypic assay which could be used as a prognostic indicator of response to 5-FU therapy in patients with colorectal cancer.

15. Claims 61-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horie and Leichman in view of Ruano, as applied to claims 47-48, 52-54, 56, 64, and 67 above, and further in view of, in the alternative, Govindarajan or Howells.

The teachings of Horie and Leichman in view of Ruano are set forth above. Horie and Leichman in view of Ruano do not specifically teach to use peripheral blood cells (blood cells, claim 64) for TS allele detection

Howells teaches a method of correlating GSTT1 null and GSTM1 null genotypes to unresponsiveness to primary chemotherapy in patients with epithelial ovarian cancer. Howells teaches genotyping for the null alleles using PCR on DNA isolated from blood, collected in EDTA, or tissue identified as macroscopically normal by the surgeon for genotyping (see abstract, p. 2440, col. 2, 4th para). Howells teaches that null alleles for both GSTT1 and GSTM1 was associated with nonresponsiveness to chemotherapy (see abstract, page 2443, col. 1, first para).

Govindarajan teaches a method using PCR to genotype the GSTM1 gene from peripheral blood cells in patients with lung cancer who had received 3 cycles of platinum based chemotherapy. Govindarajan teaches that there was a higher incidence of GSTM1 null genotypic expression in patients with SC responders (small cell cancer) as opposed to NSC responders (non small cell).

Both Howells and Govindarajan provide examples of methods for screening for sensitivity to chemotherapeutic drugs involving determining the genotype of a pre-selected gene from normal blood samples and correlating gene expression to sensitivity to the chemotherapeutic drug.

Although Leichman teaches detecting TS expression from tumor biopsies, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to determine TS genotype from a subject's peripheral blood, for example, as taught by

Govindarajan and Howells, because such method of genotype analysis is less invasive, less painful, and therefore obviously more preferable to the patient, than determining TS genotype from a biopsy. Horie teaches that the number of repeats is associated with TS expression in normal cells, therefore the teachings of Horie provide a reasonable expectation of success that accurate TS genotype analysis can obtained for a subject from normal cells.

Given that Leichman teaches that expression levels of TS correlated with sensitivity to 5-FU and that Horie teaches that 1) TS expression is associated to the number of tandemly repeated sequences in the 5' terminal regulatory region of the human TS (thymidylate synthase) gene, 2) that the number of tandemly repeated sequences (genotype) was found to be polymorphic among individuals (see abstract, and page 191, 2nd column), 3) that the number of repeated sequences was found to result in differences in expression activity of the gene, with the double repeat showing lower expression than the triple repeat, , and 4) TS genotype could be determined for a subject from normal cells, it would have been prima facie obvious to the ordinary artisan at the time the invention was made to screen for a subject's sensitivity to 5-FU by determining the genotype of the number of tandemly repeated sequences in the 5' terminal regulatory region of the TS gene obtained from a subject's biological sample for the purpose of providing a genotypic assay which could be used as a prognostic indicator of response to 5-FU therapy in patients with colorectal cancer.

Response to Arguments and Declaration

16. The response traverses the rejection and asserts that previous arguments are incorporated by reference. As all previous arguments have been addressed, the responses to arguments from

previous office actions are maintained. The response further directs attention to the declaration filed under 37 C.F.R. 1.132 by Dr. Peter V. Danenberg, which states that the invention would not have been obvious to one of skill in the art to screen for the polymorphism in the 5' UTR of the TS gene and correlate the results to sensitivity and or responsiveness to a therapeutic regimen. The declaration by Dr. Danenberg has been thoroughly reviewed but was found insufficient to overcome the rejections under 35 USC 103, for the reasons which follow.

At page 2, section 4, of the declaration Dr. Danenberg asserts that he "disagrees with the Patent Office's characterization of the teachings" of Horie. While acknowledging at section 5, that Horie teaches that a polymorphism exists in the 5' UTR of the TS gene, it is then further stated that "Horie notes that this polymorphisms may influence mRNA expression levels transcribed from the TS gene". This is not found persuasive. Horie specifically states in the abstract: "...the expression activity of the gene with the double repeat was lower than that of the gene with the triple repeat in the transient transfection assay". Further, Horie teaches at page 194, col. 1 "the fragment with one directed repeated sequence had the same expression activity as that of the parental fragment... however, the deletion of the last deleted sequence and its complementary sequence reduced the expression activity to background levels". It is then opined that Horie does not attempt to correlate the existence or absence of the polymorphism with a patient's sensitivity to any therapeutic regimen. This is found unpersuasive to overcome the rejection as the rejection did not state that Horie attempted to correlate the existence or absence of the polymorphism with a patient's sensitivity to a therapeutic regimen. The section concludes with a statement that the system employed by and reported in Horie is very different from the system described in the specification and that Horie uses an artificial system involving

in vitro analysis of cells grown in a Petri dish and therefore does not represent cells in their natural environment. Further, at section 6, it is stated that "the specification and pending claims are directed to the levels of mRNA expression isolated from patients and how these levels correlated to the polymorphisms." These arguments have been thoroughly reviewed but were found unpersuasive. Firstly, it is noted that the claims do not require any measurement of mRNA expression, and therefore any arguments regarding the teachings of the specification with regard to mRNA expression are not found persuasive as there is no nexus between these arguments and what is being claimed. The claims do not require analysis of expression of thymidylate synthase. Additionally, the declaration makes conclusory statements without providing any facts to support the assertion that the in vitro analysis of expression assays using the deleted sequences would not be expected to be correlated to expression in a natural environment, or that this result would not give at least a reasonable expectation of success that the number of repeats is correlated with expression activity of the 5' UTR. Further, the assertions made in the declaration appear to contradict statements made in the specification. For example, at page 10, lines 18-19, the specification states "Patients with triple repeat in the TS gene as expected from in vitro models had higher gene expression levels...". The specification gives more weight to in vitro models than that opined in the declaration, and supports the notion that in vivo results were expected from in vitro data with regard to expression levels and repeats. Regardless of such, the instant claims are directed to a screening method that encompasses that a subject's genotype be determined and that a correlation be made between the genotype and sensitivity to TS directed chemotherapy. The claims do not set forth any specific correlation between sensitivity and genotype.

The assertions at page 3, section 7 have been thoroughly reviewed were not found persuasive as the rejection did not state that the claims were obvious over the teachings of Horie alone.

At section 8, the declaration asserts that "the study reported [in Leichman] only relies on the overall expression level of TS in tumor cells the expression of which may be unrelated to the 5' UTR polymorphism". This argument has been thoroughly reviewed but was not found persuasive. It is clear from the teachings of Leichman that the expression level of TS is correlated to response to 5-FU. Given that Horie states "these results suggest that at least one set of the repeated sequence and its complementary sequence is necessary for the efficient expression of the hTS gene" as well as the reasonable expectation of success that repeat number is correlated with expression activity as taught by transfection assays of Horie, and the teachings of Horie that the TS repeats in humans is polymorphic, with some subjects having a double repeat, where Horie teaches for the double repeat "the expression activity of the gene with the double repeat was lower...", one of ordinary skill in the art, in view of the teachings of Horie and Leichman, in view of Ruano, would have been motivated to screen subjects to determine the genotype in the subject's sample of the 28 base pair repeat in the 5' UTR of the TS gene and to correlate the genotype with sensitivity to TS directed chemotherapy to arrive at a genotypic assay which may be used as a prognostic indicator of response to 5-FU. The teachings of Ruano, provide further motivation to screen for a correlation between the 28 base pair tandem repeat and response to 5-FU. Again, the claims do not require any mRNA expression analysis, nor do they provide for any specific outcome regarding the correlation step. While the overall TS tumor expression may not be completely attributed to the 5' UTR polymorphism, Leichman teaches

that TS expression was relative and that different mRNA levels were associated with therapeutic response. The teachings of Horie provide a reasonable expectation of success that expression level of TS is correlated to genotype, and provide a reasonable expectation that TS expression, including expression in tumors, is correlated with genotype of the repeat polymorphism. Therefore, in view of the teachings of Horie and Leichman, in view of Ruano, the ordinary artisan would have been motivated to screen for a patient's genotype and correlate such with sensitivity to 5-FU.

At section 9, the declaration asserts that neither Howels nor Govindarajan report on determining the presence of the polymorphism in the 5' UTR region of the TS gene and only involve analysis of the GST family of genes and do not discuss polymorphisms in the TS gene. This argument has been thoroughly reviewed but was not found persuasive because the teachings of Howels and Govindarajan were used to show that methods for screening for sensitivity to chemotherapeutic drugs involving determining the genotype of a pre-selected gene from normal blood samples and correlating gene expression to sensitivity to the chemotherapeutic drug were known and used in the art at the time the invention was made. It is further noted that this rejection was only made with regard to claims 61-66. The declaration further asserts that based on these references one of skill in the art would not predict that a polymorphisms in the 5' UTR of the TS gene isolated from non tumor samples would correlate with expression in a pathological cell. This argument has been thoroughly reviewed but is insufficient to overcome the rejection. Horie teaches that this polymorphism exists in humans and is detected in leukocytes, and provides a reasonable expectation of success that it is associated with expression of the gene. This polymorphism would be expected to exist in all cells including tumors

(Kawakami et al; Proc. Annu. Meet. Am. Soc. Clin. Oncol. Vol. 17, pp A1128, May 1998). The prior art provides ample motivation to screen blood samples, instead of tumors, to detect polymorphisms that affect expression as such methods are less invasive. The declaration does not provide any factual evidence to support this conclusion. Accordingly, as TS is known to be involved in 5-FU metabolism, the teachings of the prior art provide motivation to screen a patient's genotype, including blood cells, for the TS polymorphism and correlate the genotype with 5-FU therapy response. In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

17. Claims 47-48, 50, 52-54, 56, 64 and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horie and Leichman and Kawakami (Kawakami et al; Proc. Annu. Meet. Am. Soc. Clin. Oncol. Vol. 17, pp A1128, May 1998) in view of Ruano.

Horie teaches that triple tandemly repeated sequences are known to exist in the 5' terminal regulatory region of the human TS (thymidylate synthase) gene and that the number of tandemly repeated sequences was found to be polymorphic among individuals (see abstract, and page 191, 2nd column). Horie teaches that the number of repeated sequences was found to result in differences in expression activity of the gene, with the double repeat showing lower expression than the triple repeat (see abstract). Horie teaches detection in leukocytes (blood cells; claim 64) using PCR amplification surrounding the repeat region and determination of the size of amplicons to determine the repeat(s) present (pages 192-193). While Horie teaches that possible mechanisms for expression could occur at either the transcriptional or post

transcriptional level, Horie teaches that the unique repeated structure is associated with either possibility (see page 195 column 2, to page 196, column 1, 2nd para).

Horie does not teach a correlation between expression of the TS gene and sensitivity to chemotherapeutic drugs, however, Leichman et al disclose a method for determining the suitability of treating cancer in a subject with a chemotherapeutic drug (5-fluorouracil, 5-FU) by taking a biological sample of a subject and determining expression of the TS gene (see page 3224, page 3226 last para). Leichman teaches that expression levels of TS correlated with sensitivity to 5-FU in the subjects. Leichman teaches that if patients with tumor sensitivity to 5-FU can be identified before the initiation of therapy, 5-FU based treatment could be targeted to that group and would spare toxicity to patients unlikely to respond and would allow faster progress in new drug development.

Additionally, Kawakami teaches investigating the association between the TS 5' UTR tandemly repeated sequence and expression of TS in cancers. Kawakami teaches that double and triple repeats were found, along with one quadruple and one penta repeated sequence, and that patients were predominantly either heterozygous for the double and triple repeat (18), or homozygous for the triple repeat (46), and that two patients were homozygous for the triple repeat. Kawakami teaches that TS expression correlated with the number of repeats and teaches a level of 1.07 for the 2R/2R genotype, 1.38 for the 2R/3R genotype, and 2.59 for the 3Rl/3R genotype (claim 50).

Ruano teaches that genetic variability is a determinant of a patient's response to therapy. Ruano teaches that by correlating a haplotype with disease and by using genome anthologies, which are collections of a specific locus, as targets for drug screening and development, it is

possible to create a prognostic test for customizing therapy based on a patient's genotype (see column 7, lines 3-15). Further, Ruano teaches that different gene variants may be correlated to variable expression levels and that genome anthologies may comprise collections of regulatory sequences (see col. 12, lines 40-42).

Although Leichman does not teach that the expression of TS is correlated to a particular genotype, given the teachings of Kawakami and Horie, in view of Ruano, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to arrive at a method of screening a subject for sensitivity to 5-FU by determining the number of repeats in the 5' regulatory region (genotype) in each allele of the TS gene for the purposes of developing a genotypic assay for determining a subject's response to 5-FU. The ordinary artisan would have been motivated to determine if chemotherapy with 5-FU for patients with colorectal cancer or gastrointestinal cancer could be customized for patients according to their genotype, that is the number of TS repeats, because Ruano teaches to create prognostic tests for customizing therapy based on a patient's genotype. Further, Leichman also provides motivation for screening as Leichman teaches that if patients with tumor sensitivity to 5-FU can be identified before the initiation of therapy, 5-FU based treatment could be targeted to that group and would spare toxicity to patients unlikely to respond and would allow faster progress in new drug development.

Given that Leichman teaches that expression levels of TS correlated with sensitivity to 5-FU, that Horie teaches that 1) TS expression is associated with the number of tandemly repeated sequences in the 5' terminal regulatory region of the human TS (thymidylate synthase) gene, 2) that the number of tandemly repeated sequences (genotype) was found to be polymorphic among

individuals (see abstract, and page 191, 2nd column), and 3) that the number of repeated sequences was found to result in differences in expression activity of the gene, with the double repeat showing lower expression than the triple repeat, that Kawakami teaches that the 5' UTR repeat genotype correlated with TS expression levels in gastrointestinal tumors, and that Ruano provides motivation for associating a patient's genotype with sensitivity to therapy, it would have been prima facie obvious to the ordinary artisan at the time the invention was made to screen for a subject's sensitivity to 5-FU by determining the genotype of the number of tandemly repeated sequences in the 5' terminal regulatory region of the TS gene obtained from a human subject's biological sample for the purpose of providing a genotypic assay which could be used as a prognostic indicator of response to 5-FU therapy in patients with colorectal cancer.

18. Claims 61-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horie and Leichman and Kawakami in view of Ruano, as applied to claims 47-48, 50, 52-54, 56, 64, and 67 above, and further in view of, in the alternative, Govindarajan or Howells.

The teachings of Horie and Leichman and Kawakami in view of Ruano are set forth above. Horie and Leichman and Kawakami in view of Ruano do not specifically teach to use peripheral blood cells (blood cells, claim 64) for TS allele detection

Howells teaches a method of correlating GSTT1 null and GSTM1 null genotypes to unresponsiveness to primary chemotherapy in patients with epithelial ovarian cancer. Howells teaches genotyping for the null alleles using PCR on DNA isolated from blood, collected in EDTA, or tissue identified as macroscopically normal by the surgeon for genotyping (see abstract, p. 2440, col. 2, 4th para). Howells teaches that null alleles for both GSTT1 and GSTM1

was associated with nonresponsiveness to chemotherapy (see abstract, page 2443, col. 1, first para).

Govindarajan teaches a method using PCR to genotype the GSTM1 gene from peripheral blood cells in patients with lung cancer who had received 3 cycles of platinum based chemotherapy. Govindarajan teaches that there was a higher incidence of GSTM1 null genotypic expression in patients with SC responders (small cell cancer) as opposed to NSC responders (non small cell).

Both Howells and Govindarajan provide examples of methods for screening for sensitivity to chemotherapeutic drugs involving determining the genotype of a pre-selected gene from normal blood samples and correlating gene expression to sensitivity to the chemotherapeutic drug.

Although Leichman teaches detecting TS expression from tumor biopsies, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to determine TS genotype from a subject's peripheral blood, for example, as taught by Govindarajan and Howells, because such method of genotype analysis is less invasive, less painful, and therefore obviously more preferable to the patient, than determining TS genotype from a biopsy. Horie teaches that the number of repeats is associated with TS expression in normal cells, therefore the teachings of Horie provide a reasonable expectation of success that accurate TS genotype analysis can obtained for a subject from normal cells.

Given that Leichman teaches that expression levels of TS correlated with sensitivity to 5-FU, that Horie teaches that 1) TS expression is associated to the number of tandemly repeated sequences in the 5' terminal regulatory region of the human TS (thymidylate synthase) gene, 2)

that the number of tandemly repeated sequences (genotype) was found to be polymorphic among individuals (see abstract, and page 191, 2nd column), 3) that the number of repeated sequences was found to result in differences in expression activity of the gene, with the double repeat showing lower expression than the triple repeat, , and 4) TS genotype could be determined for a subject from normal cells, that Kawakami teaches that the 5' UTR repeat genotype correlated with TS expression levels in gastrointestinal tumors, and that Ruano provides motivation for associating a patient's genotype with sensitivity to therapy, it would have been prima facie obvious to the ordinary artisan at the time the invention was made to screen for a subject's sensitivity to 5-FU by determining the genotype of the number of tandemly repeated sequences in the 5' terminal regulatory region of the TS gene obtained from a human subject's biological sample for the purpose of providing a genotypic assay which could be used as a prognostic indicator of response to 5-FU therapy in patients with colorectal or gastrointestinal cancer.

Double Patenting

19. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

20. Claims 47, 48, 50, 52-54, ~~56-60~~ 56-57, 59-60 and 67 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9of copending Application No. 10/522,664. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are coextensive in scope.

The instant claims are drawn to screening subjects for sensitivity to a TS-directed chemotherapeutic drug comprising genotyping a subject's biological sample for the 28 base pair repeat polymorphism in the 5'UTR of thymidylate synthase (TS) and correlating the genotype to sensitivity to the drug. The claims include 5-FU, as well colorectal and gastric cancer. The claims ' 664 are drawn to selecting a therapeutic regimen for treating a cancer by screening a suitable cell or tissue sample for a polymorphism correlated with treatment outcome. Claim 5 is drawn to thymidylate synthase. As defined by the specification, the polymorphism includes "a tandemly repeated 28 base pair sequence in the thymidylate synthase gene's 5' UTR. Patients less likely to be responsive to treatment with a TS directed drug, e.g., 5- fluorouracil, were determined to be homozygous for this triple repeat of the tandemly repeated sequence. Patients exhibiting heterozygous genotype for a double repeat and a triple repeat of the tandemly repeated sequence. The patients most likely to respond to administration of a TS directed drug (e.g., 5-fluorouracil) are homozygous for a double repeat of the tandemly repeated sequence." Further, as defined by the '664 specification, screening includes PCR analysis to identify the TS genotype. It would have been obvious to package the reagents necessary for the PCR reaction to

determine TS genotype in kit format for the purpose of making the method more convenient to perform.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

21. Claims 61-66 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 of copending Application No. 10/522,664 in view of Horie, Howells, and Govindarajan.

The teachings of '664 are set forth above. The claims of '664 are not specifically limited to any type of biological sample, such as bodily fluids, blood cells, or peripheral blood cells (claims 61-66), however Horie teaches detecting the TS 5'UTR 28 base pair repeat polymorphism in leukocytes of normal patients. Additionally, Howells teaches a method of correlating GSTT1 null and GSTM1 null genotypes to unresponsiveness to primary chemotherapy in patients with epithelial ovarian cancer. Howells teaches genotyping for the null alleles using PCR on DNA isolated from blood, collected in EDTA, or tissue identified as macroscopically normal by the surgeon for genotyping (see abstract, p. 2440, col. 2, 4th para). Howells teaches that null alleles for both GSTT1 and GSTM1 was associated with nonresponsiveness to chemotherapy (see abstract, page 2443, col. 1, first para). Further,

Govindarajan teaches a method using PCR to genotype the GSTM1 gene from peripheral blood cells in patients with lung cancer who had received 3 cycles of platinum based chemotherapy. Govindarajan teaches that there was a higher incidence of GSTM1 null

genotypic expression in patients with SC responders (small cell cancer) as opposed to NSC responders (non small cell).

Therefor, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use a subject's normal cells, such as peripheral blood cells for the purpose of providing a less invasive method of determining a subject's TS genotype.

This is a provisional obviousness-type double patenting rejection.

Conclusion

22. No claims are allowable over the cited prior art.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Jehanne Sitton
Primary Examiner
Art Unit 1634

10/6/06